

U.S.S.N. 07/938,154
HARPOLD, *et al.*
AMENDMENT AFTER FINAL

Action inadvertently failed to address claim 99; in a telephonic discussion it was indicated this claim was allowable).

Claims 57, 58, 61, 63, 67, 71, 73, 74, 76-78, 86-90 and 99 are cancelled without prejudice herein, and claims 55, 56, 59, 60, 62, 63, 66, 68, 70, 72, 82-84, 91, 92, 97 and 98 are amended and claims 100-112 are added in order to more particularly point out and distinctly claim the subject matter that applicant regards as the invention. The amendments and new claims primarily change the form, not the substance, of the claimed subject matter.

It is respectfully submitted that entry of this amendment either places the application into condition for allowance or substantially reduces the number of issues for appeal.

New claims 100-113 were necessitated by cancellation of certain claims and the requirement for redrafting other claims in independent format. For example, Claim 53, which was rejected as allegedly reciting an improper Markush claim, has been amended and the alternative embodiments captured in separate independent claims, each directed to a single encoded nAChR subunit (see amended claims 80 and 81). The amendment of claims 80 and 81 to independent form necessitated additional dependent claims. Thus, the new claims are directed to subject matter determined to be allowable by the Examiner or are necessitated by cancellation of rejected claims that are rewritten to obviate rejections under 35 U.S.C. §112, second and fourth paragraphs. The application should be substantially in condition for allowance. Absent such finding, it is respectfully submitted that entry of this amendment substantially reduces the number of issues for appeal.

U.S.S.N. 07/938,154
HARPOLD, *et al.*
AMENDMENT AFTER FINAL

STATUS OF RELATED CO-PENDING APPLICATIONS

It is herein brought to the attention of the Office that copending U.S. application Serial No. 08/496,855, filed June 20, 1995 has been allowed and the issued fee has been paid.

It is also noted that no obviousness-type double patenting issues should exist as between the above-noted allowed application and the instant application. Because a terminal disclaimer has been filed in this application with respect to issued U.S. Patent No. 5,369,028, any issue of obviousness-type double patenting as between the instant application and the allowed copending application is moot. It is also noted that as between the copending allowed application and the instant application, obviousness-type double patenting was not found.

CORRECTION OF THE FILING RECEIPT AND FILING DATE OF THE APPLICATION AS ENTERED INTO THE PALM SYSTEM

It is respectfully submitted that the filing date (102(e) date) of the above-captioned application is incorrectly entered into the PALM system as being April 3, 1991. April 3, 1991 is the International filing date of this application. The 35 U.S.C. §102(e) date of this application should be the date of completion of the requirements for entering the National Stage in the U.S., which was November 30, 1992.

Attention is directed to the Decision on the Petition under 37 C.F.R. §1.181, dated January 7, 1997 and the Decision on the Petition under 37 C.F.R. §1.181, dated February 22, 1994. The Decision in 1997 dismissed the Petition as unnecessary because the decision on the Petition Under 37 C.F.R. §1.181, dated February 22, 1994, granted the application the correct 102(e) date of November 30, 1992. In that paper, it indicated that the case was being forwarded to Applications Division so that a corrected filing receipt would be issued. A new filing receipt was issued, but the date is again incorrectly

U.S.S.N. 07/938,154
HARPOLD, *et al.*
AMENDMENT AFTER FINAL

entered as April 3, 1991, which is the international filing date of the PCT application of which this application is the national stage.

The Decision on Petition Under 37 C.F.R. §1.181, dated February 22, 1994, page 2, states under the heading "Conclusion" that this application will be given a date of 30 November 1992 under 35 U.S.C. §371(c) and 102(e).

In the Amendment mailed February 20, 1997, the Examiner's assistance in correcting the filing date of the subject application was requested. A Second Request for Corrected Official Filing Receipt was mailed April 30, 1997. No response to this request has been recieved.

Even more disturbing, the Office Action Summary mailed June 26, 1997, indicates that the filing date is **November 30, 1995**, which is now off by three years. It appears that a failed attempt was made to correct the PALM records related to this application.

Therefore, after several failed attempts, the aid of the Examiner in obtaining a corrected filing receipt that reflects the correct national stage filing date of November 30, 1992 is respectfully requested.

THE REJECTION OF CLAIMS 53-57, 58-63, 66-68, 70, 72-74, 76, 77, 86-92 AND 95 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 53-57, 58-63, 66-68, 70, 72-74, 76, 77, 86-92 and 95 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. The various bases for this rejection are discussed in turn below. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks.

Relevant law

35 U.S.C. §112, second paragraph requires only reasonable precision in delineating the bounds of the claimed invention. The claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. Shatterproof

U.S.S.N. 07/938,154
HARPOLD, *et al.*
AMENDMENT AFTER FINAL

Glass Corp.v. Libby-Owens Ford Co., 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir), cert dismissed, 106 S. Ct. 340 (1985).

The amount of detail required to be included in the claims depends on the particular invention and the prior art and is not to be viewed in the abstract, but in conjunction with whether the specification is in compliance with the first paragraph of 35 U.S.C. §112. If the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more. Scripps Clinic & Research Foundation v. Genentech Inc. 18 USPQ 1001 CAFC 1991).

a) Claims 53, 54 and 58

Claims 53, 54 and 58 are rejected as allegedly reciting an improper Markush group. In the interests of advancing prosecution of this application, claims 54 and 58 are cancelled without prejudice and claim 53 as amended does not recite alternative embodiments.

It is respectfully submitted that, however, that the claims did not recite Markush groups, but rather recited nucleic acid encoding each subunit as an alternative. "Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims." [see MPEP 2173.05(h), see also, In re Wolfrum 486 F.2d. 588, 179 USPQ 620 (CCPA 1971), which held that Section 112 cannot serve as the basis for rejecting a single claim on the ground that it embodies more than one invention (i.e., alternative)]. A Markush group is just one type of alternative form of expression. The alternatives set forth in the instant claims are not intended to be a Markush group. MPEP 2173.01 states:

A fundamental principle contained in 35 U.S.C. 112, second paragraph is that applicants are their own lexicographers. They can define in the claims what they regard as their invention essentially in whatever terms they choose so long as the terms are not used in ways that are contrary to accepted meanings in the art. Applicant may use functional language,

alternative expressions, negative limitations, or any style of expression or format of claim which makes clear the boundaries of the subject matter for which protection is sought. As noted by the Court in *In re Swinehart*, 439 F.2d 210, 160 USPQ 226 (CCPA 1971), a claim may not be rejected solely because of the type of language used to define the subject matter for which patent protection is sought.

Thus, a claim reciting alternative expressions is acceptable as it is unambiguous. In this instance, there is not ambiguity.

b) Claims 55, 56 and 72

Claims 55, 56 and 72 are allegedly incorrect because there is no antecedent basis for "the" sequence of amino acids encoded by the referenced nucleotide sequences. In the interests of advancing prosecution of this application, claims 55 and 56 are cancelled herein, rendering the rejection moot as to these claims. With respect to claim 72, although the propriety of this rejection remains in question, in the interests of advancing prosecution, the specified language has been deleted from claim 72 and claim 72 has been amended to recite "a" sequence of amino acids with reference to the deposited material.

c) Claim 57

Claim 57 is also rejected because a nucleic acid cannot hybridize to a nucleic acid sequence. Claim 57, however, did not recite a nucleic acid sequence, but rather recited a "sequence of nucleotides"; nucleotides are material entities. DNA can hybridize to nucleotides. Again, in the interests of advancing the prosecution of this application, claim 57 is cancelled herein.

d) Claims 59-61

Claims 59-61 are rejected as being indefinite in failing to provide antecedent basis for "nucleic acids." Each of claim 59 and 60 is amended to recite nucleic acid molecule of claim", thereby reciting language for which antecedent is clearly provided.

e) Claim 66

Claim 66 is rejected as being indefinite for being drawn to "The of claim 59." Claim 66 as amended recites "the cell of claim 59".

f) Claim 67

Claim 67 is rejected as being indefinite in failing to provide antecedent basis for "The cell of claim 66." Claim 67 has been cancelled, rendering the rejection moot.

g) Claims 73, 74 and 86

Claims 73, 74 and 86 are rejected because the language "substantial homology" is allegedly indefinite because it has no clear meaning in the art. In the interests of advancing prosecution of this application, claims 73, 74 and 86 are cancelled without prejudice.

First it is respectfully noted that claims are read in light of the specification and the term "substantial" is only if definite if the specification does not provide a standard for measuring the degree intended:

The phrases "relatively shallow," "of the order of," "the order of about 5 mm," and "substantial portion" were held to be indefinite because the specification lacked some standard for measuring the degree intended and, therefore, properly rejected as indefinite under 35 U.S.C. 112, second paragraph. *Ex parte Oetiker*, 23 USPQ2d 641 (Bd. Pat. App & Inter. 1992). In this instance, however, the specification does provide a definition (see page 12, lines 16-33):

Use of the phrase "substantial sequence homology" in the present specification and claims means that DNA, RNA or amino acid sequences which have slight and non-consequential sequence variations form the actual sequences disclosed and claimed herein are considered to be equivalent to the sequences of the present invention, and as such are within the scope of the appended claims. In this regard, "slight and non-consequential sequence variations" mean that "homologous" sequences (*i.e.*, the sequences that have substantial sequence homology with the DNA, RNA, or proteins disclosed and claimed herein) will be functionally equivalent to the sequences disclosed and claimed in the present invention. Functionally equivalent sequences will function in substantially the same manner to produce substantially the same compositions as the nucleic acid and amino acid compositions disclosed and claimed herein.

U.S.S.N. 07/938,154
HARPOLD, *et al.*
AMENDMENT AFTER FINAL

Thus it is clear what is intended by the term "substantial homology".

Second, the term substantial homology has an art recognized meaning. A search of the LEXPAT database revealed countless instances in which the term is defined in a manner similar to that set forth above. Furthermore, a search of the claims yielded 63 patents in which the term "substantial homology" or substantially homologous is set forth in a claim. These patents include U.S. Patent Nos. 4,511,652, 4,751,081, 4,766,073, 4,769,328, 4,798,885, 4,801,541, 4,801,542, 4,849,407, 4,886,754, 4,889,802, 4,894,333, 4,908,203, 4,918,006, 4,918,166, 4,933,288, 4,940,840, 4,952,499, 4,971,952, 5,008,240, 5,013,644, 5,023,078, 5,034,323, 5,045,471, 5,084,390, 5,124,255, in which this term is used to define the relationship between nucleic acid molecules or between proteins.

The fact that this language appears in claims in patents that issued prior to the filing date or around the time of the filing date of the instant application evidences that those of skill in the art would understand the language in the claim.

The caselaw holds that the use "substantially" is not of itself fatal. Eibel Process Co. v. Minnesota & Ontario Paper Co., 261 U.S. 45, 67 L. Ed. 523, 43 S. Ct. 322 (1923); use of "substantial" to describe an angle of pitch of a paper-making machine was sufficiently definite on the ground that those skilled in the art would know what was meant).

indeed, it must always be implied in every claims, even when not introduced, and adds nothing when it is. Were this not true, few patents could be given any protection, for some departures from the precise disclosure are nearly always possible without losing the benefit of the invention. Musher Foundation v. Alba Trading Co., 150 F.2d 885, 66 USPQ 183 (2d Cir. 1945), cert. denied, 326 U.S. 770 (1945).

h) Claim 92

U.S.S.N. 07/938,154
HARPOLD, *et al.*
AMENDMENT AFTER FINAL

Claim 92 is rejected as indefinite because of the word "comprisinga."
The word "comprisinga" has been deleted from claim 92, rendering the rejection moot.

THE REJECTION OF CLAIMS 55, 56, 76, 77, 82-84 AND 98 UNDER 35 U.S.C. §112, FOURTH PARAGRAPH

Claims 55, 56, 76, 77, 82-84 and 98 are rejected under 35 U.S.C. 112, fourth paragraph, as being improperly dependent for allegedly failing to limit the claim upon which each depends. In the interests of advancing prosecution of this application, claims 55, 56, 76, 82-83 and 98 are cancelled herein, and claims 77, 84 and 98 are rewritten in independent form. Thus, the rejection is moot with respect to all the rejected claims.

It is noted, however, that the claim structure of these claims prior to amendment was proper. The MPEP (608.01(n)) states that a dependent claim does not have to further limit the claim from which it depends, but rather must include all limitations in the claim from which it depends.

The test for a proper dependent claim is that:

... it shall include every limitation of the claim from which it depends (35 U.S.C. 112, fourth paragraph) or in other words that it shall not conceivably be infringed by anything which would not also infringe the basic claim.

A dependent claim does not lack compliance with 35 U.S.C. 112, fourth paragraph, simply because there is a question as to (1) the significance of the further limitation added by the dependent claim, or (2) whether the further limitation in fact changes the scope of the dependent claim from that of the claim from which it depends. The test for a proper dependent claim under the fourth paragraph of 35 U.S.C. 112 is whether the dependent claim includes every limitation of the claim from which it depends. *The test is not one of whether the claims differ in scope.* [emphasis added, see MPEP 608.01(n)].

Thus, claims 55, 56, 76, 77, 82-84 and 98 are properly dependent because each of these claims "includes every limitation of the claim from which it [each] depends".

Finally it is noted, that this application is the national stage of an international PCT application. Where national and international rules conflict, international rules should apply. In international practice dependent claims are preferred over independent claims.

THE REJECTION OF CLAIMS 53-63, 66-68, 70-77, 86, 88-92 AND 95-98 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 53-63, 66-68, 70-77, 86, 88-92 and 95-98 are rejected under 35 U.S.C. § 112, first paragraph, because the disclosure is allegedly for claims limited to a nucleic acid encoding one of the subunits that is encoded by the biological material that was deposited as described in lines 10 to 14 on page 19 of the instant specification for those reasons of record in section 7 of Paper Number 26. This rejection is respectfully traversed insofar as it applies to any of the presently pending claims.

It is respectfully submitted that cancellation of claims 59, 60, 62, 66, 68, 70, 72, 76-78, 86-90, and 95 renders this rejection moot with respect to these claims. Claims 55, 56, 62, 63, 66, 91, 92 and 96-98 remain rejected. It is respectfully submitted that pending claims are **directed nucleic acid molecules encoding one of the subunits that is encoded by the biological material** that was deposited or to a subunit encoded by SEQ ID No. 9, which the specification teaches is a full-length sequence. Therefore, the claims are of the scope that the Examiner urges is enabled.

For example, The Examiner urges that claim 97 encompasses a nucleic acid encoding a beta2 subunit of a human nicotinic acetylcholine receptor and that the term "nicotinic acetylcholine receptor" is a class of receptors. The term "beta2 subunit of a human nicotinic acetylcholine receptor" is defined in the text in lines 34 to 31 on page 11 of the instant application, but which does not

allegedly identify properties of a beta2 subunit. The Examiner urges that no reading frame is given. The sequence listing indicates that the coding sequence is 1-1521, and inspection of the sequence reveals that the first codon is an ATG, and the last is a stop codon. Therefore, the open reading frame is apparent on the face of the sequence.

It is respectfully submitted that claim 97, which is directed to the nucleic acid molecule described in the specification as encoding a full length beta2 subunit and degenerate variants thereof. Claim 97 recites:

An isolated nucleic acid molecule, comprising a sequence of nucleotides that encodes a beta2 subunit of a human nicotinic acetylcholine receptor, wherein the beta2 subunit comprises the sequence of amino acids encoded by the sequence of nucleotides set forth as nucleotides 1-1521 in SEQ ID No. 9. The properties of a beta2 subunit that distinguish it from a structurally related protein are irrelevant with respect to this claim, which is directed to the sequence of nucleotides set forth in SEQ ID No. 9 and degenerate variations thereof.

In the interests of advancing prosecution of this application, claims 55-63, 66, 67, 71, 73-76, 86, 88-91, and 96-98 are cancelled without prejudice and claims 68, 72, 77 and 92 are amended to recite nucleic acid encoded by the encoding DNA of the deposited plasmids. With respect to claims 70 and 95, it is respectfully submitted that the rejection is moot in view of the amendment of claim 68.

Relevant law

In order to satisfy the enablement requirement of 35 U.S.C §112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409. This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not

U.S.S.N. 07/938,154
HARPOLD, *et al.*
AMENDMENT AFTER FINAL

require "a specific example of everything within the scope of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973). Rather, the requirements of §112, first paragraph "can be fulfilled by the use of illustrative examples or by broad terminology." In re Marzocchi et al., 469 USPQ 367 (CCPA 1971), emphasis added.

Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960). Thus, there is no doubt that a patentee's invention may be broader than the particular embodiment shown in the specification. A patentee is not only entitled to narrow claims, particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

Thus, there is no requirement for disclosure of every species within a genus. Applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the claimed invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman,

U.S.S.N. 07/938,154
HARPOLD, *et al.*
AMENDMENT AFTER FINAL

230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

A. It would not require undue experimentation to make and use the claimed DNA fragments and cells

As stated above, the inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the claimed invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

As discussed below the claims are commensurate in scope with the disclosure, which exemplifies particular embodiments within the scope of the claims and also teaches how one of skill can obtain other embodiments within the scope of the claims.

The level of skill in the art is high

The level of skill in this art is recognized to be high (see, e.g., Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). In addition, the numerous articles and patents that are of record in this application that are authored by those of a high level of skill for an audience of a high level of skill further evidences the high level of skill in this art. Thus, those of skill in the art would be able to obtain the deposited material, sequence it, compare it to the disclosed sequences and identify the open reading frame encoding an α_3 -subunit, or a beta2 subunit, for which the entire sequence is provided in the instant application. Those of skill in the art can recognize an open reading

frame by looking for start and stop codons. Those of skill in this art also could readily use the deposited clones and disclosed DNA molecules to isolate related clones from human DNA libraries.

The scope of the claims

The claims encompass nucleic acid that encodes the subunits encoded by the deposited clones and degenerate variants thereof and nucleic acid that can be readily isolated using the instantly disclosed nucleic acid.

Claim 53 recites:

An isolated nucleic acid molecule, comprising a sequence of nucleotides encoding a beta2 subunit of a human neuronal nicotinic acetylcholine receptor.

The instant specification provides a full-length clone and the sequence thereof that encodes a beta2 subunit of a human neuronal nicotinic acetylcholine receptor. The instant applicant is the first to have isolated DNA encoding human neuronal nicotinic acetylcholine receptors, and, thus, is entitled to claims of breadth that will dominate others who use the disclosure of the instant application to isolate related clones. Granting claim 53 will not preclude others from obtaining patent coverage on any specific variants, but will reward the instant applicant for having first isolated this subunit and having provided a full-length sequence.

Claim 55 recites:

An isolated and purified subunit of the human neuronal nicotinic acetylcholine receptor encoded by the alpha3-encoding nucleic acid in a plasmid having all of the identifying characteristics of HnAChR α 3 deposited under ATCC Accession No. 68278.

To practice this claim, the skilled artisan would only have to obtain the deposited clone, introduce the DNA from the clone into a host a cell and express the encoded molecules. It would not even be necessary to isolate the nicotinic acetylcholine receptor subunit-encoding portion of from the cloned DNA, since such the open reading frame would be expressed. Alternatively, the

specification provides substantial sequence information (see SEQ ID Nos. , which set forth portions of the $\alpha 3$ -encoding nucleic acid) and restriction maps, so that the $\alpha 3$ -encoding portion could be readily identified, and introduced into a host for expression, or sequenced and translated to obtain the encoded $\alpha 3$ subunit sequence.

Claims 56 and 99 similarly recite:

56. An isolated and purified subunit of the human neuronal nicotinic acetylcholine receptor encoded by the beta2-encoding nucleic acid in a plasmid having all of the identifying characteristics of HnAChR $\alpha 3$ deposited under ATCC Accession No. 68279.

98. An isolated and purified beta2 subunit of a human nicotinic acetylcholine receptor encoded by a nucleic acid molecule, comprising a sequence of nucleotides that encodes a beta2 subunit of a human nicotinic acetylcholine receptor, wherein the beta2 subunit comprises a sequence of amino acids encoded by the sequence of nucleotides set forth in SEQ ID No. 9.

To practice these claims, the skilled artisan would only have to obtain the deposited clone or nucleic of SEQ ID No. 9, introduce the nucleic from the clone or that of SEQ ID No. 9 into a host a cell and express the encoded molecule. It would not even be necessary to isolate the nicotinic acetylcholine receptor subunit-encoding portion of from the cloned DNA, since such the open reading frame would be expressed. Alternatively, the specification provides the full-length sequence (see SEQ ID No. 9, which sets forth the open reading frame that encodes a beta2 subunit), so that the beta2-encoding portion could be readily identified, and introduced into a host for expression.

Upon issuance of a patent claiming the deposited material, those of skill in the art will have unrestricted access thereto, and could readily use such DNA to obtain degenerate codons and/or to obtain the encoded subunits. As discussed below, it would be unfair and unduly limiting not to grant the instant applicant claims that encompass the deposited DNA, degenerate variants thereof, and encoded subunits.

Claim 62 recites:

The cell of claim 60 that is a eukaryotic cell.

Claim 60 is directed to an isolated cell, comprising [containing one or more of] the nucleic acid molecule of claim 81; and claim 81 is directed to:

an isolated nucleic acid molecule, comprising a sequence of nucleotides encoding a beta2 subunit of a human nicotinic acetylcholine receptor that is encoded by the beta2-encoding nucleic acid that is isolated from a plasmid having all of the identifying characteristics of HnAChR β 2 deposited under ATCC Accession No. 68279 or the open reading frame set forth in SEQ ID No. 9.

Claim 81 has been deemed allowable, and, thus is enabled. It would not require any experimentation to introduce the nucleic acid of claim 80 into a cell.

Claim 63 is directed to:

The cell of claim 59 that is a bacterial cell, mammalian cell, yeast cell or amphibian oöcyte.

where claim 59 is directed to an isolated cell, comprising the nucleic acid molecule of claim 80, and claim 80 is directed to:.

An isolated nucleic acid molecule, comprising a sequence of nucleotides encoding an alpha3 subunit of a human nicotinic acetylcholine receptor that is encoded by the alpha3-encoding nucleic acid that is isolated from a plasmid having all of the identifying characteristics of HnAChR α 3 deposited under ATCC Accession No. 68278.

Claim 80 was only rejected under 35 U.S.C. §112, second paragraph, because of its dependence upon claim 57. As amended claim 80 is an independent claim that should be allowable. It is respectfully submitted that it would not require any experimentation to introduce alpha3-encoding nucleic acid obtained from the deposited material into a cell in light of the sequence information and restriction maps provided in the specification.

Claim 66 recite:

The cell of claim 59 further comprising a nucleic acid molecule that encodes a beta subunit of a human nicotinic acetylcholine receptor, wherein the beta subunit comprises a sequence of amino acids encoded by SEQ ID No. 9.

Claim 59 is discussed above. It would not require any experimentation to introduce a nucleic acid molecule comprising SEQ ID No. 9 or a degenerate variant thereof into the cell of claim 59.

Claims 91 and 92

Claim 91 is directed to the cell of 59 that further comprises a reporter gene construct, and claim 92 is directed to a method of testing that uses the cell of claim 91.

Claim 59 is discussed above. Introduction of a reporter gene construct into a cell does not require any experimentation, nor does use of the cell in a method in which the cell is contacted with a test compound.

Claims 96 and 97

Claim 97 is discussed above. As noted above, SEQ ID No. 9 encodes an open reading frame and claim 97 specifies the reading frame.

Claim 96 is directed to:

An isolated nucleic acid molecule, comprising the sequence of nucleotides set forth in SEQ ID No. 9.

No knowledge of a reading frame nor structural properties of a subunit is required to practice claim 96. All that is require is SEQ ID No. 9, which is provided in the specification.

The claims are, thus, directed to nucleic acid molecules, encoded proteins, and cells can be readily obtained from the disclosure of the specification. The claims encompass the specifically disclosed DNA, the deposited DNA and DNA that can be constructed by substituting degenerate codons for the codons in the disclosed or deposited DNA, and DNA that encodes minor, but equivalent, amino acid alternations, such as DNA that

encodes a protein that includes a single conservative amino acid change. The specification provides the deposited material, sequence information and restriction maps from which open reading frames are readily apparent or can be readily identified in light of the knowledge and level of skill of those in this art.

Teaching and guidance in the specification

In addition, there is guidance presented in the specification for isolating DNA, there are deposited clones that comprise DNA that encodes all or a substantial portion (5 nucleotides are missing from the deposited α_2 -encoding clone) of each subunit. Also, partial or complete sequences of each subunit are set forth in the specification.

The specification teaches how to introduce the DNA encoding the subunits into host cells, express such DNA to produce functional heterologous nicotinic acetylcholine receptors and test such for activity. Thus, the specification provides sufficient guidance to permit those of skill in the art to ascertain identify open reading frames in the deposited clones and determine which of those encode a subunit.

Patents are written to enable those of skill in the art to practice the invention. A patent need not disclose what is well known in the art (W.L. Gore & Assoc. v. Gorlock, Inc., 721 F.2d 1540, 1556, 220 USPQ 303, 315). In this instance, those of skill in the art would have access to the deposited DNA and would be able, if necessary, to sequence the DNA encoding each subunit and/or to use the deposited clones to readily isolate other such clones. The specification defines (page 11, lines 7-31) what is encompassed by the DNA encoding each subunit. Further, the specification teaches that the both subunits are required for formation of a functional ligand-gated channel. The specification teaches DNA encoding each of the subunits and provides deposits that contain this DNA and also, as discussed above, defines what is intended for each DNA clone encoding the each subunit to encompass.

One of skill in this art could readily obtain the deposited clones or obtain nucleic acid including nucleotides of the sequence set forth in the figures and one of skill in this art could readily substitute degenerate codons for the codons set forth in the figures or the codons in the deposited DNA. The nucleic acid can be identified by comparison with the sequence of the disclosed or deposited DNA and by inclusion of an open reading frame that encodes one of the specified subunits. If necessary the DNA can be introduced into cells and used to produce functional receptors whose activity can be assessed as exemplified in the application.

There is no requirement that the specification teach how the instant applicant achieved its particular result (unless there is evidence that the applicant believed that its way constitutes the best mode; deposit of the clones satisfies the best mode issue). Furthermore, in this instance, the specification does teach how these clones were identified and teaches that the isolated clones can be used to isolate related clones. Starting at page 12, about line 12, the specification teaches:

by probing numerous human cDNA libraries, e.g., pre-frontal cortex cDNA, parietal cDNA, temporal cortex cDNA, brain stem cDNA, basal ganglia cDNA, and spinal cord cDNA, various fragments of the human neuronal subunits were identified (see, for example, Figures 4, 5 and 6). After partial sequencing and restriction mapping of several such fragments . . . it was possible to identify composite DNA sequences for the human neuronal alpha2, alpha3 and beta2 subunits, as disclosed and claimed herein.

In addition to their use as coding sequences for the production of human neuronal subunits and synthetic human neuronal receptors, the invention sequences can also be used as probes for the identification of additional human neuronal sequences. This is done by probing various sources of human neuronal DNA with invention sequences, then selecting those sequences having a significant level of sequence homology with the probe employed.

Thus, the specification also teaches that the deposited clones can be used to isolate related clones.

Also, the specification does provide sequence information regarding DNA and, thus, the encoded proteins. Sequence ID Nos. 1, 3, 5, 7 and 9 set forth nucleic acid sequences of each of the subunits. **SEQUENCE ID NO. 9 sets forth the entire coding sequence for the beta 2 subunit.** The specification also provides restriction maps of the deposited clones. It would not require undue experimentation to use the disclosed DNA and/or the deposited clones as probes to identify and isolate closely related (*i.e.*, substantially homologous) DNA molecules.

Conclusion

Therefore, in light of the scope of the claims, the level of skill in the art, the knowledge of those of skill in this art, the teachings in the specification, the provision of deposited clones, it would not require undue experimentation for one of skill in the art to make and use the claimed subject matter.

Furthermore, it is unfair and unduly limiting to require applicant to limit the claims to only specifically disclosed embodiments. To do so is contrary to the public policy upon which the U.S. patent laws are based. If applicant is required to limit the claims to only the deposited plasmids, then those of skill in the art could by virtue of these deposits isolate DNA encoding closely related subunits or readily modify deposited DNA by substitution of degenerate codons and practice what is disclosed in the application, but avoid infringing such limited claims. To permit that is simply not fair. The instant application teaches nucleic acid encoding $\alpha 3$ and $\beta 2$ subunits of a human neuronal nicotinic acetylcholine receptor and thereby provides a means for others to isolate such subunits. As is apparent from the specification and the DECLARATION, this was clearly not a routine task, but required creative invention to have obtained the clones. Thereafter, having such clones, permits one of skill to readily isolate related clones. Thus, the disclosure and the deposits permit others to readily clone nucleic acid encoding such subunits or to make minor changes in deposited DNA and thereby avoid infringement.

Certainly, applicant is entitled to claims to the deposited plasmids and/or to the portion of each plasmid that comprises DNA that encodes all or a portion of a nicotinic acetylcholine receptor subunit and is entitled to claims that encompass the disclosed nucleic acid fragments and degenerate variations thereof, cells containing such nucleic acids and methods using the cells. Applicant is the first to have isolated any human nicotinic acetylcholine receptor-encoding nucleic acid, and as such should be entitled to claims directed thereto.

- B. The instant claims are not analogous to claim 7 in U.S. Patent No. 4,703,008, which was deemed invalid under 35 U.S.C. §112, first paragraph, as not being enabled by the specification

First, it is noted that enablement is determined by reference to the teachings in the specification and the knowledge of those of skill in the art at the time of filing (such knowledge is presumed to be part of the application disclosure). Thus, a finding that a claim is of analogous scope to one deemed non-enabled in one case, has no relevance to the case at issue, since enablement is a function of the teachings in the specification. As discussed below (B), the instant specification teaches how to make and use what is claimed without undue experimentation.

Assuming, arguendo, that such determination is relevant, it is respectfully submitted that the instant claims are not analogous to claim 7 of U.S. Patent No. 4,703,008, but rather are more analogous to claim 2, which was deemed valid.

Briefly, Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 18 USPQ2d 1016, (CAFC 1991) (hereinafter, Amgen or Amgen v. Chugai) concerns the infringement and validity of two patents, U.S. Patent No. 4,703,008, assigned to Amgen, Inc. and U.S. Patent No. 4,677,195, assigned to Genetics Institute (hereinafter, the '008 and '195 patents, respectively). One of the court's considerations in this case was the validity of claims 2 and 7 of

U.S.S.N. 07/938,154
HARPOLD, *et al.*
AMENDMENT AFTER FINAL

the '008. Claim 2 was challenged as obvious in view of the prior art and was held valid by the court. Claim 7 was challenged as lacking enablement under 35 U.S.C. § 112 and was held to be invalid by the court.

The claims at issue here are very different from the claim in the Amgen patent to which the Examiner refers. Claim 7 in U.S. Patent No. 4,703,008 reads:

7. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.

Claim 7, thus, reads, not only on peptides encoding erythropoietin but also on other peptides, erythropoietin analogs, *i.e.* peptides with "EPO-like" activity (see, Amgen Inc. v. Chugai Pharmaceutical Co. Ltd. at 1028), that have a similar sequence such that they possess two biological properties in common with erythropoietin. The Court found that the claims encompass analogs of erythropoietin and that Amgen had failed to find any erythropoietin analogs that possess both requisite biological properties. In addition, the supporting language in the specification defined the DNA fragments to include any that hybridize; the language of the instant claims that is more limited and is not intended to encompass alpha2-like-, alpha3-like- and beta2-like-encoding DNA.

Thus, the claims are more narrowly drawn than those at issue in Amgen Inc. v. Chugai Pharmaceutical Co. Ltd. and are more analogous to claim 2 of Amgen, which has been held valid. Claim 2 recites:

A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding erythropoietin.

In this instance, most of the claims at issue herein are more limited than claim 2 of Amgen, since the instant claims include sequence limitations and functional limitations. In addition, the instant specification provides for definitions of the intended scope of the claims. Also, claim 7 of patent at issue in Amgen

defined the encoded DNA with reference to the biological activity of the encoded protein; the specified biological activities do not necessarily uniquely define erythropoietin. Thus, the claim was held to encompass erythropoietin analogs.

With respect to invalidated claim 7, the court held that "it (was) not sufficient, having made the gene and a handful of analogs whose activity (had) not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity," Amgen v. Chugai, 18 USPQ2d 1016 at 1028, emphasis added. The court also states, however, that "[i]t is well established that a patent applicant is entitled to claim his invention generically, when he describes it sufficiently to meet the requirements of Section 112," directing attention to Utter v. Hiraga, 845 F.2d 993, 998, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988); and In re Robins, 429 F.2d 452, 456-457, 166 USPQ 552, 555 (CCPA 1970). Thus, claim 2 of the '008 patent, directed to "DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin," was properly enabled by the specification.

Furthermore, the specification defines all terms used in the claims and clearly sets forth the intended scope contemplated by each term. As established below, the claims do not encompass DNA encoding any and all such receptors but a clearly defined and readily obtainable subset thereof. Therefore, the specification is not comparable to that in U.S. Patent No. 4,703,008, in defining the intended scope of claim 7.

As noted above, the instant claims are more narrowly drawn than that at issue in Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.. First, the instant claims are limited to DNA encoding the human neuronal NACHR α_2 , α_3 or β_2 subunits and to cells containing the DNA. Thus, the claims are limited to DNA encoding particular subtypes of each receptor subunit. The DNA includes DNA having substantially the same sequence as the deposited DNA and DNA that encodes subunits that have substantially the same sequence as the subunits encoded by

the deposited plasmids or that encode proteins that include the sequences of amino acids set forth in the figures.

THE REJECTION OF CLAIMS 55, 56, 76-78 and 82-84 UNDER 35 U.S.C. §102(B)

Claims 55, 56, 76-78 and 82-84 are rejected under 35 U.S.C. §102(b) as being clearly anticipated by Whiting *et al.* because the limitation "isolated" allegedly only requires any state of purity that is higher than that which occurs in nature. It is noted that claim 78 was previously cancelled in the Amendment mailed February 20, 1997. This rejection is respectfully traversed.

Whiting *et al.* describes a sucrose gradient fraction that contains partially purified human nicotinic acetylcholine receptors. Whiting *et al.* does not teach isolation or purification of human nicotinic acetylcholine receptor subunits, nor such isolated and purified subunits. Figure 5B in Whiting *et al.* noted by the Examiner shows sucrose gradient analysis of human brain AChR. This figure does not show any isolated subunits of the human AChR. There is no structural analysis set forth in Whiting *et al.* of human neuronal nicotinic acetylcholine receptor subunits.

Nowhere in the specification nor in the art of record is "isolated" defined to encompass "any state of purity higher than occurs in nature." No basis for this interpretation is provided. Clearly, the instant claims are intended to encompass isolated subunits, not subunits in sucrose gradient fraction that contains partially purified receptor fraction.

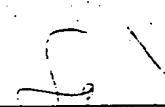
Therefore, since anticipation requires disclosure of all elements of a claim under consideration in a single prior art reference, Whiting *et al.*, which does not disclose purification or isolation of any human neuronal nicotinic acetylcholine receptor subunits, cannot anticipate any of claims 55, 56, 77 and 82-84.

U.S.S.N. 07/938,154
HARPOLD, *et al.*
AMENDMENT AFTER FINAL

* * *

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
BROWN, MARTIN, HALLER & McCLAIN

By: 
Stephanie L. Seidman
Registration No. 33,779

Attorney Docket No. 6362-9380
Address all correspondence to:
BROWN, MARTIN, HALLER & McCLAIN
1660 Union Street
San Diego, California 92101-2926
Telephone: 619/238-0999
EMAIL sseidman@BMHM.com